Complete Summary

GUIDELINE TITLE

Recommendations for the management of BCR-ABL-positive chronic myeloid leukaemia.

BIBLIOGRAPHIC SOURCE(S)

Goldman J. Recommendations for the management of BCR-ABL-positive chronic myeloid leukaemia. London (UK): British Committee for Standards in Haematology; 2007. 14 p. [18 references]

GUIDELINE STATUS

This is the current release of the guideline.

** REGULATORY ALERT **

FDA WARNING/REGULATORY ALERT

Note from the National Guideline Clearinghouse: This guideline references a drug(s) for which important revised regulatory and/or warning information has been released.

- July 31, 2008, Erythropoiesis Stimulating Agents (ESAs): Amgen and the U.S. Food and Drug Administration (FDA) informed healthcare professionals of modifications to certain sections of the Boxed Warnings, Indications and Usage, and Dosage and Administration sections of prescribing information for Erythropoiesis Stimulating Agents (ESAs). The changes clarify the FDA-approved conditions for use of ESAs in patients with cancer and revise directions for dosing to state the hemoglobin level at which treatment with an ESA should be initiated.
- November 8, 2007 and January 3, 2008 Update, Erythropoiesis Stimulating Agents (ESAs): The U.S. Food and Drug Administration (FDA) notified healthcare professionals of revised boxed warnings and other safety-related product labeling changes for erythropoiesis-stimulating agents (ESAs) stating serious adverse events, such as tumor growth and shortened survival in patients with advanced cancer and chronic kidney failure.

COMPLETE SUMMARY CONTENT

SCOPE

DISEASE/CONDITION(S)

BCR-ABL-positive chronic myeloid leukemia (chronic myelogenous leukemia, chronic myelocytic leukemia, CML)

GUIDELINE CATEGORY

Diagnosis
Management
Treatment

CLINICAL SPECIALTY

Hematology
Oncology

INTENDED USERS

Physicians

GUIDELINE OBJECTIVE(S)

To provide recommendations for the diagnosis and management of patients with *BCR-ABL*-positive chronic myeloid leukemia

TARGET POPULATION

Patients in the United Kingdom with *BCR-ABL*-positive chronic myeloid leukemia

INTERVENTIONS AND PRACTICES CONSIDERED

Evaluation

1. Full blood count with microscopic differential
2. Bone marrow aspirate and trephine biopsy with cytogenetics and real-time quantitative reverse transcriptase (RQ-PCR) for *BCR-ABL* transcripts
3. Peripheral blood fluorescence in situ hybridization (FISH) for presence of *BCR-ABL* and possible deletion in the der(9) chromosome
4. Neutrophil alkaline phosphatase (not recommended)

5. Human leukocyte antigen typing for patient and family (if patient is aged less than 65 years)
6. Peripheral blood stem cell collection and cryopreservation (not recommended)
7. Classification of disease phase
8. Estimation of prognosis using Sokal, Euro, or Hasford prognostic score

Treatment

1. Imatinib as first-line therapy
2. Bone marrow transplantation in children with an appropriate matching donor
3. Second-line therapy with dasatinib, nilotinib, bosutinib, MK-0457
4. Third-line therapy with interferon-alfa or hydroxycarbamide
5. Allogeneic bone marrow transplantation for second-line therapy failure or patients with T3151 subclone

Management

1. Treatment of drug side effects (e.g. drug interruption, erythropoietin, granulocyte colony-stimulating factor, corticosteroids)
2. Assessment of treatment response or failure (follow-up FISH, RQ-PCR, hematology, marrow cytogenetics, kinase domain mutations)
3. Frequency of follow-up bone marrow cytogenetics

MAJOR OUTCOMES CONSIDERED

- Rate of remission
- Duration of survival
- Severity of adverse effects
- Sensitivity of real-time quantitative reverse transcriptase

METHODOLOGY

METHODS USED TO COLLECT/SELECT EVIDENCE

Searches of Electronic Databases

DESCRIPTION OF METHODS USED TO COLLECT/SELECT THE EVIDENCE

Not stated

NUMBER OF SOURCE DOCUMENTS

Not stated

METHODS USED TO ASSESS THE QUALITY AND STRENGTH OF THE EVIDENCE

Not stated

RATING SCHEME FOR THE STRENGTH OF THE EVIDENCE

Not applicable

METHODS USED TO ANALYZE THE EVIDENCE

Review

DESCRIPTION OF THE METHODS USED TO ANALYZE THE EVIDENCE

Not stated

METHODS USED TO FORMULATE THE RECOMMENDATIONS

Expert Consensus

DESCRIPTION OF METHODS USED TO FORMULATE THE RECOMMENDATIONS

In this rapidly moving field of *BCR-ABL*-positive chronic myeloid leukemia treatment, to produce formal evidence-based guidelines was considered impossible. Instead, 'recommendations' were based on past experience and recently published results of the use of tyrosine kinase (TK) inhibitors on both sides of the Atlantic, which were hoped to be valid for at least a year after their publication.

RATING SCHEME FOR THE STRENGTH OF THE RECOMMENDATIONS

Not applicable

COST ANALYSIS

A formal cost analysis was not performed and published cost analyses were not reviewed.

METHOD OF GUIDELINE VALIDATION

Not stated

DESCRIPTION OF METHOD OF GUIDELINE VALIDATION

Not applicable

RECOMMENDATIONS

MAJOR RECOMMENDATIONS

Evaluation at Diagnosis

Confirmation of Diagnosis

It is always important to confirm the suspected diagnosis of Philadelphia (Ph)-positive chronic myeloid leukemia (CML). Essential investigations include a full blood count ideally with a 1000 cell differential performed by microscopy, a bone marrow aspirate and trephine biopsy together with bone marrow cytogenetics and real-time quantitative reverse transcriptase (polymerase) chain reaction (RQ-PCR) for *BCR-ABL* transcripts. Fluorescence in situ hybridization (FISH) studies on a peripheral blood will confirm the presence of a BCR-ABL gene but can also be designed to detect a possible deletion in the der(9) chromosome. Neutrophil alkaline phosphatase is no longer routinely measured. HLA typing for the patient and family members may prove useful if the patient is aged less than 65 years. It is not currently recommended that peripheral blood stem cells should routinely be collected and cryopreserved at diagnosis, but a number of research laboratories in the United Kingdom (UK) appreciate receiving cells (after appropriate approval from their Research Ethics Committee and relevant informed consent have been obtained).

Assessing the Phase of Disease

It is conventional to classify a patient's disease at the time of diagnosis as chronic phase, accelerated phase or blastic transformation, though in some cases categorisation can be extremely difficult. Accelerated and blastic phases may be grouped together as advanced phase. Criteria for defining the three phases of CML have been proposed by the International Bone Marrow Transplant Registry (IBMTR), the MD Anderson Cancer Center in Houston and by the World Health Organisation (WHO); the criteria specified for the purposes of the studies using tyrosine kinase (TK) inhibitors differ to a minor degree from all three. In general the MD Anderson classification restated in the recent Leukemia-Net publication is used most widely (see Table 1 of the original guideline document). The WHO classifies as accelerated phase a patient with cytogenetic evidence of clonal evolution in the absence of any other criteria of acceleration; such a patient would be classified as chronic phase by Leukemia-Net criteria.

Estimating Prognosis

The Sokal prognostic score, which takes into account a patient's age, spleen size, percentage of blood blasts and platelet count was introduced in 1984 and was derived from survival figures for patients treated predominantly with busulphan. The Euro or Hasford score is a modification of the Sokal score that incorporates also basophil and eosinophil numbers; it is based on assessment of patients treated primarily with interferon. Preliminary experience suggests that these scoring systems can still discriminate when patients are treated with imatinib, but molecular characterisation, e.g. gene profiling may eventually prove more informative.

Initial Management

Patients Presenting in Chronic Phase

There is general agreement that the majority or all patients who present with chronic phase (CP) disease should be treated initially with imatinib or in the context of a clinical study with an imatinib-containing regimen. The possible exceptions are a child who has a human leukocyte antigen (HLA)-identical sibling

or a patient fortunate enough to have a syngeneic twin. Economic considerations may also dictate choice of therapy outside the UK; thus for a patient in a developing country who might be unable to pay for imatinib on a long-term basis a single payment for transplantation could be the more realistic option.

The standard starting dose is 400 mg/day for an adult. It may be that starting treatment at a lower dose, e.g. 100 or 200 mg/day, encourages the development of drug resistance and should therefore be avoided. Reports from the MD Anderson Cancer Center show more rapid cytogenetic and molecular responses with a starting dose of 800 mg/day but this higher dose is not always well tolerated and does not demonstrably prolong survival. The two dose levels, 400 mg/day and 800 mg/day, are now being compared in prospective studies in Europe and North America. Until results of these trials are available, 400 mg day may be the best approach for a patient not entered into a clinical trial.

Grade 3/4 adverse effects are relatively rare with standard dose imatinib but lesser degrees of toxicity are not uncommon. They include rashes, bone pain, fluid retention, anorexia, depression, weight gain and other symptoms. Myelosuppression may necessitate temporary interruption of therapy but may respond to haemopoietic growth factors including erythropoietin and granulocyte colony-stimulating factor (G-CSF). Use of short term corticosteroids may be indicated for treatment or prevention of rashes or abnormal levels of hepatic enzymes.

Patients Presenting in Advanced Phase

Patients presenting with advanced phase disease who will not previously have been exposed to imatinib may be treated initially with imatinib at 600 or 800 mg/daily. For those with blastic transformation who initially respond the duration of response may be short and continuing treatment immediately after initial response should involve use of conventional chemotherapy with or without an allogeneic stem cell transplant.

Patients Progressing to Advanced Phase

For patients whose disease progressed to advanced phase while they were taking imatinib, there is no logic to continuing the same drug. They may respond to one or other of the second generation of TK inhibitors. Allogeneic stem cell transplantation should be considered if feasible if a suitable donor can be identified.

Monitoring Patients on Imatinib

Cytogenetics and FISH

Patients in chronic phase who achieved complete haematological remission with interferon-alfa were in the past monitored with regular bone marrow aspirates to assess the level of Ph-negativity or less commonly with FISH studies to detect the presence of the *BCR-ABL* fusion gene in peripheral blood cells. Now that 80% or more of patients with CML in CP treated ab initio with imatinib achieve a complete cytogenetic remission, it is logical to perform routine bone marrow examinations,

perhaps every 3 months, only until complete cytogenetic remission (CCyR) is achieved and then to rely principally on the much more sensitive RQ-PCR for *BCR ABL* transcripts. Some experts recommend continuing to perform bone marrow aspirates for cytogenetic studies at one year intervals even in responding patients to detect possible clonal abnormalities in Ph-negative cells but their clinical significance is not clear and it may not be essential if transcripts number remain low.

Real-time Quantitative PCR for *BCR-ABL* Transcripts

The mainstay for monitoring patients who seem to be responding to treatment should be RQ-PCR for *BCR-ABL* transcripts. The technology is demanding and results from laboratories where the test is done relatively infrequently are quite often unreliable. An attempt is now being made to standardise use of control genes. Eventually internationally validated reference reagents will be available but until that time it is hazardous to compare directly numerical values between different laboratories. For a patient whose response seems to be slow, bone marrow cytogenetic analysis may be repeated at three month intervals.

It was agreed at the Bethesda meeting convened by the National Institutes of Health (NIH) in October 2005 that the optimal way of expressing results of measuring *BCR-ABL* transcripts was to use the ratio of *BCR-ABL* transcript copy numbers to the number of transcript copies of a suitable control gene converted to a percentage. The alternative would be to express copy numbers as a log reduction from a laboratory specific standardised baseline value of 100%, though this method also would not take adequate account of the patients own baseline level. By this method a value of 1% (or lower) would be regarded as a 2 log reduction and usually consistent with CCyR and a value of 0.1% (or lower) would be a 3 log reduction and has been termed a 'major molecular response.' The term complete molecular remission has been used but this takes no account of the fact that the sensitivity of the assay may vary substantially in different laboratories; the term 'undetectable transcripts' may be preferable.

Frequency of Testing

For the patient who seems to be responding, measuring *BCR-ABL* transcripts in a reliable laboratory is arguably the single most important method for monitoring response. It might be informative to repeat the bone marrow aspirate for cytogenetics at 3 months after starting treatment with imatinib, but the level of Ph-positivity can in fact be extrapolated with reasonable accuracy from knowledge of the transcript levels and by six months most patients should have achieved a CCyR. At that point further estimates of the quantity of residual disease must be based on results of RQ-PCR, which typically has a sensitivity of 1 in 10^5 or even 1 in 10^6. FISH provides little useful information after a patient has achieved CCyR. **A reasonable recommendation is that for the responding patient *BCR-ABL* transcript levels should be measured at three month intervals indefinitely**. There is a case for performing routine marrow cytogenetic studies at 12 month intervals in patients believed to be in continuing CCyR; this will identify clonal cytogenetic abnormalities in the Ph-negative population, the clinical significance of which is undetermined.

If the level of *BCR-ABL* transcripts appears to be rising, the test should be repeated as soon as convenient without waiting the full three months. If the repeat test shows that the level has risen by 0.5 or 1.0 log the next step should be to search for kinase domain mutations in the same cyclic DNA (cDNA) that was used for RQ-PCR and to examine the bone marrow for Ph-positive cells and clonal evolution. The additional information gained from these tests will contribute to the therapeutic decision.

Imatinib Response and Failure

Definitions (see Table "Definitions of Response to Treatment" below)

On the assumption that a patient with CML starts treatment with imatinib as a single agent, the factors that must be considered for assessing response are (a) Duration of treatment, (b) Technology employed, i.e. blood counts, cytogenetics/FISH and RQ-PCR, and (c) Actual dosage consumed by the patient. Each technology has various 'landmarks' which can be defined with varying degrees of accuracy, i.e.

Haematology: Complete haematological remission implies resolution of splenomegaly (if previously present), restoration of normal blood counts and loss of marrow hypercellularity

Marrow cytogenetics: The absence or proportion of persisting Ph-positive marrow metaphases defines a CCyR (or CCgR), a partial cytogenetic response (PCyR or PCgR)) and a minor haematological response. Taken together CCyR and PCyR are referred to as a major cytogenetic response (MCyR).

RQ-PCR: A 3-log reduction is referred to as a major molecular response. The absence of detectable transcripts is sometimes referred to as a complete molecular remission (CMolR) but the term 'undetectable transcripts' is preferred since it implies that the level of detection or nondetection depends on the sensitivity of the assay (see above).

Kinase domain mutations: The clinical significance of *BCR-ABL* kinase domain (KD) mutations is not yet clear. Some are clearly associated with resistance to imatinib and one mutation, coding for a threonine to isoleucine substitution at position 315 (T315I), produces a sub-clone resistant both to imatinib and to dasatinib and nilotinib. Patients with such mutations may be eligible for treatment with one of the third generation of TK inhibitors. Conversely other mutations that remain at low levels for long periods may be insignificant.

Definition of Response

Responses may be defined at the haematological, cytogenetic and/or molecular levels and these are of course dependent on time from starting treatment and drug dosage. The terminology recommended by Leukemia-net for describing haematogical, cytogenetic and molecular responses is summarised in the table below. Patients failing to satisfy one or other of these criteria at a given time point are classified as non-responders (see 'Definitions of Failure' below).

Table: Definitions of Response to Treatment

Haematologic Response (HR)	Cytogenetic Response (CyR)		Molecular response (MolR)	
Complete (CHR)		*Ph-pos metaphases*		
Platelets <450 x 10^9/L	*Complete (CCyR)*	0%	*Complete*	Transcripts not detectable
WBC <10 x 10^9/L	*Partial (PCyR)*	1-35%		
Differential: No immature granulocytes and <5% basophils	*Minor*	36-65%	*Major*	0.1%
	Minimal	66-95%		

Notes:

1. The complete and partial cytogenetic response rates may be combined and referred to as the major cytogenetic response (MCyR) rate.
2. A major molecular response is equivalent to a 3-log reduction from a standardised baseline value of 100%.
3. The term 'Transcripts not detected' or 'Transcripts not detectable' is preferred to 'Complete molecular remission'.
4. There is no current agreement as to whether RQ-PCR technology is as sensitive as nested PCR and thus whether the finding of undetectable transcripts by RQ-PCR needs to be confirmed with nested PCR.

Definition of Failure

The European Leukemia-Net has recently proposed that patients at diagnosis or after starting treatment with imatinib should be classified into one of three categories. The criteria for the categories, which may in fact overlap to some extent, are specified in Table 3 of the original guideline document and the clinical implications of these categories are:

a. Failure – Indicates that imatinib should be discontinued and some other treatment initiated.
b. Sub-optimal response – Indicates that treatment with imatinib should be reassessed and treatment may be changed immediately or in the foreseeable future
c. Warnings – A patient has features at diagnosis or developing during treatment that suggest that his/her leukemia may become resistant to imatinib and/or progress to advanced phase and therefore needs closer monitoring than average.

Options for Further Management

It is difficult to make a firm recommendation for how to continue treatment for the patient judged to have failed first-line imatinib. This will depend in part on whether the patient is still in chronic phase or is in advanced phase. For the patients still in chronic phase there are a number of possible options (listed in the table below) but in practice only the first three are relevant in the first instance. For a patient who is taking imatinib 400 mg daily it is reasonable to increase the dose to 600 or even 800 mg daily and this will reverse the features of resistance in some cases; usually however the response is transient and another avenue will need to be explored. The encouraging results with use of dasatinib for patients resistant to or intolerant of imatinib mean that this agent should probably be standard second-line treatment for imatinib failure, though allogeneic stem cell transplant can be considered for the younger patient with an HLA-identical sibling donor. It is likely that nilotinib will be licensed soon in the UK and this agent may prove just as effective as dasatinib. Bosutinib may also prove valuable for such patients though it is not yet widely available. If however the patient fails to respond well to dasatinib (or nilotinib) or if he/she proves to have a T315I mutant subclone, then a transplant should be considered even in the absence of a matched sibling. The aurora kinase inhibitor MK-0457 may be active in patients with the T315I subclone but its clinical value is not yet established. A reasonable third line alternative for a patient still in chronic phase who is resistant to both imatinib and dasatinib would be interferon-alfa or hydroxycarbamide.

Table: The Various Options That Can Be Considered for the Patient Deemed TO Have Failed Initial Treatment with Imatinib

- Simply increasing the dose of imatinib
- Switching to a second line agent, e.g. dasatinib, nilotinib, bosutinib, or MK-0457
- Allogeneic stem cell transplantation, with conventional or possibly reduced intensity conditioning
- Classical cytotoxic drugs, e.g. cytarabine, hydroxycarbamide (hydroxyurea), busulphan, homoharringtonine, decitabine, arsenicals, or interferon-alfa
- Experimental agents, e.g. downstream signal transduction inhibitors such as farnesyl transferase inhibitors, mTOR inhibitors, PI3K inhibitors
- Autografting with cells collected at diagnosis or after achieving CCyR
- Immunotherapeutic strategies

CLINICAL ALGORITHM(S)

None provided

EVIDENCE SUPPORTING THE RECOMMENDATIONS

TYPE OF EVIDENCE SUPPORTING THE RECOMMENDATIONS

The type of supporting evidence is not specifically stated for each recommendation.

BENEFITS/HARMS OF IMPLEMENTING THE GUIDELINE RECOMMENDATIONS

POTENTIAL BENEFITS

Reduced morbidity and mortality

POTENTIAL HARMS

- It may be that starting imatinib treatment at a lower dose, e.g. 100 or 200 mg/day, encourages the development of drug resistance and should therefore be avoided. Reports from the MD Anderson Cancer Center show more rapid cytogenetic and molecular responses with a starting dose of 800 mg/day but this higher dose is not always well tolerated and does not demonstrably prolong survival.
- Grade 3/4 adverse effects are relatively rare with standard dose imatinib but lesser degrees of toxicity are not uncommon. They include rashes, bone pain, fluid retention, anorexia, depression, weight gain and other symptoms. Myelosuppression may necessitate temporary interruption of therapy but may respond to haemopoietic growth factors including eryrthropoietin and granulocyte colony-stimulating factor (G-CSF). Use of short term corticosteroids may be indicated for treatment or prevention of rashes or abnormal levels of hepatic enzymes.

QUALIFYING STATEMENTS

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While the advice and information in these guidelines is believed to be true and accurate at the time of going to press, neither the authors, the British Society for Haematology nor the publishers accept any legal responsibility for the content of these guidelines.

IMPLEMENTATION OF THE GUIDELINE

DESCRIPTION OF IMPLEMENTATION STRATEGY

An implementation strategy was not provided.

INSTITUTE OF MEDICINE (IOM) NATIONAL HEALTHCARE QUALITY REPORT CATEGORIES

IOM CARE NEED

Living with Illness

IOM DOMAIN

Effectiveness

IDENTIFYING INFORMATION AND AVAILABILITY

BIBLIOGRAPHIC SOURCE(S)

Goldman J. Recommendations for the management of BCR-ABL-positive chronic myeloid leukaemia. London (UK): British Committee for Standards in Haematology; 2007. 14 p. [18 references]

ADAPTATION

Not applicable: The guideline was not adapted from another source.

DATE RELEASED

2007

GUIDELINE DEVELOPER(S)

British Committee for Standards in Haematology - Professional Association

SOURCE(S) OF FUNDING

British Committee for Standards in Haematology

GUIDELINE COMMITTEE

Not stated

COMPOSITION OF GROUP THAT AUTHORED THE GUIDELINE

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FINANCIAL DISCLOSURES/CONFLICTS OF INTEREST

Not stated

GUIDELINE STATUS

This is the current release of the guideline.

GUIDELINE AVAILABILITY

Electronic copies: Available from the British Committee for Standards in Haematology Web site.

Print copies: Available from the British Committee for Standards in Haematology; Email: bcsh@b-s-h.org.uk.

AVAILABILITY OF COMPANION DOCUMENTS

None available

PATIENT RESOURCES

None available

NGC STATUS

This NGC summary was completed by ECRI Institute on March 17, 2008. The information was verified by the guideline developer on April 1, 2008. This summary was updated by ECRI Institute on August 15, 2008 following the U.S. Food and Drug Administration advisory on Erythropoiesis Stimulating Agents (ESAs).

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